IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Vera Afremova
Art Unit	:	1651
Appellant	:	John Ernest Hart
Serial No.	:	09/856,944
Filed	:	May 30, 2001
Confirm. No.	:	6466
For	:	Isolated Material Having an Anti-Organotrophic Effect

Mail Stop Appeal Brief-Patents
Honorable Commissioner of Patents
Attention: Board of Patent Appeals and Interferences
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

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TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

This application is owned by Endocrine Pharmaceuticals Limited.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF THE CLAIMS

Claims 1, 3-6, 8 and 11-14 are pending in this application and stand finally rejected under 35 U.S.C. §103(a). Claims 1, 3-5, 8 and 11-13 stand rejected under 35 U.S.C. 102(b) as anticipated by U.S. Patent No. 4,734,398, or, in the alternative, under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 4,734,398. Also, claims 1, 3-6, 8 and 11-14 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 4,734,398. The §102/§103 rejections of claims 1, 3-5, 8 and 11-13, as well as the §103 rejections of claims 1, 3-6, 8 and 11-14 are appealed herein.

IV. STATUS OF AMENDMENTS

In an Amendment dated September 10, 2004, the Applicants canceled claims 2, 7, 9-10, 16 and withdrew claims 15, 17-21. The September 10, 2004 Amendment was entered leaving claims 1, 3-6, 8 and 11-14 pending. In the final Office Action dated November 24, 2004, claims 1, 3-6, 8 and 11-14 were finally rejected. The claims as currently pending are attached hereto in Appendix A.

V. SUMMARY OF THE INVENTION

The subject invention is a unique and advantageous material that reduces the mass of non-gonadal organs in live adult mammals. This material is found in a purified 10-30 kD sub-fraction of mammalian ovarian venous blood.

VI. ISSUES

A. Whether claims 1, 3-5, 8, 11-13, which are directed to a material that reduces the mass of body organs, including non-gonadal organs of a live adult mammal, and that is inducible by clomiphene and obtained by purifying post-oestrus ovarian venous blood, are anticipated by, or obvious in view of, U.S. Patent No. 4,734,398, which describes a material having a similar molecular weight but which is obtained from a different source and has different properties.

B. Whether claims 1, 3-6, 8, 11-14, which are directed to a material that reduces the mass of body organs, including non-gonadal organs of a live adult mammal, and that is inducible by clomiphene and obtained by purifying post-oestrus ovarian venous blood, are obvious over U.S. Patent No. 4,734,398, which does not teach or even suggest a material having the advantageous characteristics of the subject material.

VII. GROUPING OF CLAIMS

The claims stand or fall together.

VIII. ARGUMENT

A. Claims 1, 3-5, 8, 11-13, which are directed to a material that reduces the mass of body organs, including non-gonadal organs of a live adult mammal, and that is inducible by clomiphene and obtained by purifying post-oestrus ovarian venous blood, are not anticipated by, or obvious in view of U.S. Patent No. 4,734,398, which describes a material having a similar molecular weight but which is obtained from a different source and has different properties.

The subject invention is a unique and advantageous material that reduces the mass of non-gonadal organs in live adult mammals. This material, which is inducible by clomiphene, is found in a purified 10-30 kD sub-fraction of mammalian ovarian venus blood collected post-oestrus.

The Appellant has claimed this material in terms of its molecular mass, its source, and its salient biological properties. In rejecting the Appellant's claims, the Final Office Action cites a single reference — the diZerega reference. The diZerega reference discloses a material whose molecular mass falls within the range set forth in the Appellant's claim; however, the diZerega material does not possess multiple other characteristics of the Appellant's claimed material. These additional characteristics provide a definite characterization of the claimed material such that it can be readily distinguished from the diZerega material.

As discussed below, because the diZerega material does not possess (explicitly or inherently) the characteristics set forth in the Appellant's claims, a finding of novelty for the Appellant's claims is compelled. Furthermore, there is no teaching, guidance, or suggestion in the diZerega reference as to how one skilled in the art would arrive at the Appellant's material. Therefore, the Appellant's material, as claimed, is also non-obvious in view of diZerega.

The Appellant's claims have several very specific limitations that are not met by the diZerega reference. Each of these limitations is discussed below:

1. The material must be inducible post-oestrus by clomiphene.

Clomiphene is a well-known non-steroidal ovulatory stimulator. Although clomiphene is known to stimulate ovulation in humans when administered under certain conditions, in the current

case the claimed material has been found to be induced by clomiphene independent of ovulation. This limitation is set forth in the claim by reciting that the claimed material is inducible "post-oestrus" by clomiphene and is obtained in post-oestrus ovarian venous blood. Because clomiphene does not re-induce ovulation, it is clear that the presence of the claimed material in post-oestrus ovarian blood is not a consequence of ovulation.

In an Office Action dated May 13, 2004 the examiner states at page 7 that "the claimed invention encompasses a material that is required to be isolated from ovarian venous blood of a mammal that is in the phase of ovulation or that is induced to ovulate by clomiphene."(emphasis added) This statement incorrectly characterizes the current invention because, as required by the claims, the claimed material must itself be inducible by clomiphene post-oestrus.

As explained in Prof. Clarke's Expert Declaration dated 26 July 2004, the Appellant's claimed material (a.k.a. "micrin") is induced by clomiphene at any time during the oestrus cycle and the induction of the claimed material is not caused by ovulation:

> 6. Clomiphene is known to induce ovulation, if provided over a prolonged period of time, in women who are not ovulating. However, if sheep are provided with an acute administration of clomiphene within a few days after ovulation has occurred, as described in the present patent application, this certainly does not cause further ovulation. The reproductive system is refractory to re-ovulation induction at this time, because the sheep would be in the luteal phase of the oestrous cycle, when progesterone levels are high; this prevents ovulation.
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>
> 8. On the other hand, clomiphene does appear to induce the production of micrin, at whatever phase of the oestrous cycle it is administered. Micrin induction by clomiphene does not appear to be a secondary effect of ovulation, as it occurs whenever clomiphene is administered and regardless of when ovulation has occurred.

Therefore, because administration of clomiphene post-oestrus does not induce re-ovulation, the Appellant's material, which is found in post-oestrus blood after administration of clomiphene, is clearly directly inducible by clomiphene.

In addressing Prof. Clarke's Expert Opinion as it relates to this claim limitation, the Final Office States at page 7:

> [t]he characteristics of the claimed compound and/or feature of the claimed invention such as being inducible by clomiphene and/or collection from post-oestrus female mammals do [sic] appear to be critical and distinguishable features of the claimed invention over the prior art since the prior art material is collected around ovulation time and, thus, it would be induced by clomiphene that induces ovulation and/or because the cited material(s) or materials with 10-20 kD would be present or collected in a least some amounts in female mammal post-oestrus or after ovulation.

To the extent that this sentence/paragraph is comprehensible at all, it is technically inaccurate (because clomiphene does not induce ovulation post-oestrus) and certainly does not provide any sound basis for concluding that diZerega teaches a material that is inducible post-oestrus by clomiphene.

2. The claimed material reduces the mass of organs, including non-gonadal organs, of a live adult mammal.

This claim limitation has three aspects: a) a reduction of organ mass, b) including non-gonadal organs, and c) in live adult mammals. The diZerega reference does not teach <u>any</u> of these aspects. Each of these three claim limitations is addressed in detail below.

a. Reduction of organ mass

The Final Office Action incorrectly states (at, for example, page 2) that diZerega's FRP "has the ability to reduce organ mass". diZerega's FRP does not cause weight reduction of anything, in absolute terms; it merely suppresses a weight gain that would otherwise have occurred in a particular experimental situation involving ovarian enlargement. On those occasions where diZerega uses phrases that could be construed as indicating a true decrease in ovarian weight (e.g. column 10 line 48), diZerega is clearly using this language to refer to <u>a decrease in the increase</u> that would otherwise have occurred. This is evident from a reading of the description (rather than picking out a phrase in isolation), and is also evident from the numerical values given for ovarian weight.

In considering this issue from the perspective of one skilled in the art, it is first necessary to understand the experimental test protocol that diZerega was using. This is explained in detail

starting at column 9 line 50 to column 10 line 33. The biological assay used 23-day- old immature rats that were initially subjected to hypophysectomy – that is, removal of the pituitary – and then given an implant containing DES. A well established effect of hypophysectomy is a reduction in ovarian mass, as is reported in Hart ("Pituitary-related weight changes affecting the liver, uterus and adrenal glands of rats treated with hexoestrol and clomiphene in high doeses" (1990) *Toxicology* 61:185-194). This effect is due to the absence of pituitary gonadotropins. Forty-eight hours after hypophysectomy, diZerega gave the rats varying concentrations of gonadotropins (such as hMG) and in some cases test fractions, and 24 hours later the animals were sacrificed and the ovaries weighed. Figure 1 shows how the ovarian weight changed in response to hMG. The initial weight was 21.2 mg, and this was seen to increase with the dose of gonadotropin to a maximum of 46 mg. Having carried out this preliminary test, "[o]ne international unit of hMG injected every 12 hours for two days was chosen as the challenge regimen in the bioassay." (column 10 lines 27-30)

Example 1 relates to the identification of FRP from ovarian venous blood taken during the preovulatory stage (column 8 lines 63-67 and column 9 line 13, and column 10 line 35). This blood was treated to select FRP by various steps including eluting fractions, and the fractions were tested in the bioassays. "When these eluents were tested in the bioassays, the combined rat ovarian weights ranged from 57-100 mg . . . fractions with a Ve/Vo of 1.42-1.55 corresponded to an inhibition of hMG-induced ovarian stimulation in the bioassay, as evidenced by a decrease in ovarian weight (59 mg) ..." (column 10 lines 41-48). (emphasis added) The emphasized phrase is the one quoted by the examiner, yet it is clear that there is no actual decrease in ovarian weight (59 mg for two ovaries is more than double the initial weight of 21.2 mg). This phrase merely highlights that hMG-induced ovarian stimulation (which, as shown in figure 1, leads to an ovarian weight gain) has been inhibited – consequently the ovarian weights increase by less than they would have done without the FRP. That is to say, the weight increase (which in Example 1 had gone from 21.2 mg up to 46 mg for each ovary) is decreased.

In the rest of that paragraph there is similar inconsistency in phraseology, although the meaning remains clear:

> Peripheral and ovarian venous blood... demonstrated similar G-50 elution profiles ... However, when ... tested by bioassay, no reduction in ovarian weight ... was found. Further, ovarian venous blood preparations from the anovulatory patients

> also failed to suppress the response of the ovaries to hMG stimulation. However, ovarian venous sera from the ovulatory ovary of patients 2 and 3 had a similar ... elution profile. Fractions with a Ve/Vo of 1.48-1.60 suppress the response of rat ovarian weight . . . to hMG stimulation ... When active fractions from the G-50 eulents of patients 1-3 were heated or tripsin digested, they lost their ability to suppress ovarian weight ... in response to HMG stimulation." (column 10 line 52 – column 11 line 2)

Figure 3 shows the dose response curve of "ovarian weight suppression" in the DES-treated rat ovaries by fractions from patient 1; again, there is no suggestion that the weights of the ovaries decreased: in every case the values are at least 25 mg (see upper graph), which is greater than the initial weight of 21.2 mg.

Example 2 describes further studies to evaluate the role of FRP. Again, the activity was determined by "inhibition of human menopausal gonadotropin induced ovarian weight gain ... in hypophysectomised, DES-treated, 25 day old female rats." (column 12 lines 13-19). In the Example the material was obtained from human follicular fluid, rather than venous blood. The bioassay procedure is further explained at column 14 lines 1-11:

> "Control determinations (no injected test fractions) for unstimulated ovarian weight were 34.7 mg/rat and for LH-FSH-stimulated were 192 mg/rat ... Where indicated, 100% inhibition equals ovarian weight ... of mean, unstimulated control values. Zero percent inhibition equals ovarian weight...of LH-FSH-stimulated control rats."

Thus, in every case the ovarian weight either remains constant or increases: "100% inhibition" means that the ovarian weight remains at the unstimulated value (34.7 mg per rat [= about 17.3 mg per ovary]).

Example 3 describes further experiments using material obtained from follicular fluid. The bioassay was as described previously, and "[r]esults of control determinations (no injected test fractions) were 34.8 mg/rat for unstimulated ovarian weight and 122.0 mg/rat for FSH-stimulated ovarian weight" (column 16 lines 39-44).

diZerega himself summarised the findings as: "[i]n Examples One through Three protein(s) in ovarian venous effluent... inhibited rat ovarian weight gain in response to gonadotropin stimulation." [column 20 lines 29-33]. (emphasis added) Thus diZerega's FRP does not have the capability of

reducing organ mass; it merely has the capability of inhibiting the increase of ovarian mass as caused by the gonadotropins in the artificial situation of hypophysectomised rats.

The Appellant's claims require the material to cause a decrease in the mass of body organs. This is a very surprising property, and quite different to that of FRP, a local modulator of gonadotropin action. The ability to reduce organ mass is explicitly required by the Appellant's claims; this characteristic is absent from the diZerega teachings.

b. Reduction in mass of non-gonadal organs

After misconstruing diZerega's teachings with regard to FRP's effect on ovaries, the Final Office Action addresses, at page 6 and 7, the ability to reduce mass of non-gonadal organs by stating:

> [a]pplicant also argues that since the combined effect of gonadotropins and "FRP" primary [sic] relates to gonadal organs, there is no reasonable grounds to expect that the cited material {diZerega' compound or "FRP" as argued} would reduce non-gonadal organ mass as the applicant's "micrin" could or would. Although it might be true for chemical compounds established as "FRP" and "micrin", the chemical structure and the link between structure and biological function of the applicant's material is poorly characterized as claimed and as disclosed in order to distinguish the applicant's material from the material(s) as disclosed by the cited diZerega's patent. The only known fact or the only evidence is that structure (molecular weight) of both materials is identical. Therefore, arguments based on some unidentified and/or undisclosed characteristics do not provide sufficient grounds for the evidence to the contrary to the claim rejection under 35 U.S.C. 102(b) . . .

Again to the extent that this is comprehensible at all, the Final Office Action appears, in effect, to ignore this vital limitation completely and simply reiterate that the materials have similar molecular weights (indeed, going so far as to describe the molecular weights as 'identical', when in each case molecular weights are simply given as falling within a wide range). As to reducing the masses of non-gonadal organs, no data are presented in diZerega relating to the actual reduction of any organ mass, gonadal or non-gonadal. Ignoring a key limitation, non-gonadal action, does not negate its presence in the claim or the filaure of the cited reference to disclose a material having this property. Accordingly, a finding of anticipation and/or obviousness is improper.

c. Reduction of organ mass in a live adult mammal.

After careful scrutiny of the Final Office Action, the Appellant has yet to identify where this aspect of the claim is addressed at all. Suffice it to say, diZerega does not teach or suggest a material meeting this claim limitation. diZerega uses non-intact (surgically altered) immature mammals, achieving no reduction in ovarian mass. In contrast, the Appellant's claimed material achieves reduction in ovarian and other organ masses using intact live adult mammals.

3. The material is purified from venous ovarian blood collected from a mammal post-oestrus.

In addressing this issue the examiner makes the following observations:

> "[di Zerega's] [b]lood collection is done on days 12-14 after last menstrual period that is around ovulation period"; (Final Office Action, page 3)

and

> "Furthermore, the starting material of the cited patent is collected about the period of ovulation . . ." (emphasis added) (Final Office Action, page 3)

Perhaps sensing that these statements do not constitute convincing evidence of anticipation or obviousness, the examiner concludes with:

> Or, the starting collected material is considered to be the same regardless cycle timing of ovarian blood collection because the starting collected material would contains at least some amounts of the material(s) as intended whether it is collected during ovulation and post-oestrus. (Final Office Action, page 3)

Again, the Appellant respectfully submits that, to the extent that this statement can be understood at all, it does not provide a basis for concluding that diZerega discloses a material meeting the limitations of the Appellant's claims.

Blood collection for FRP on days 12-14 after the onset of the last menstrual period, as described by diZerega, corresponds to pre-ovulatory sampling, appropriate for a postulated mid-cycle gonadotropin modulator. In contrast, micrin is obtained on day 6 after ovulation (i.e. post-oestrus).

Of course, for an anticipation rejection to be proper, a single prior art reference must disclose, within its four corners, each and every element of the claimed invention. In *Dewey & Almy Chem. Co. v. Mimex Co.*, Judge Learned Hand wrote:

> No doctrine of the patent law is better established than that a prior patent . . . to be an anticipation must bear within its four corners adequate directions for the practice [of the subsequent invention] . . . if the earlier disclosure offers no more than a starting point . . . if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation. 124 F.2d 986, 990; 52 USPQ 138 (2nd Cir. 1942).

The present invention is directed to a material inducible by clomiphene, that reduces organ mass of non-gonadal organs in live adult mammals, and which is obtained post-oestrus. Such a material is not disclosed, or even suggested, by diZerega. Because the diZerega reference does not disclose, within its four corners, a composition having the characteristics recited in the current claims, an anticipation rejection is improper.

With regard to obviousness, the Final Office Action states that even if the claimed material differs from diZerega with regard to some "unidentified characteristics" then:

> . . . the differences between that which is disclosed and that which is claimed are considered to be so slight that the referenced material and/or fractions are likely to inherently possess the same characteristics of the claimed material...(emphasis added) (Final Office Action, page 4)

Of course, "inherency" is a concept most commonly applied in the context of an anticipation rejection. In any event, it is abundantly clear that a rejection based upon inherency (either anticipation or obviousness) is improper in the current case.

Under the Patent Laws, a prior art rejection based on inherency is only proper if the prior art necessarily (not "likely," as stated by the examiner) resulted in the claimed subject matter. *In re King*, 801 F2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986). Further,

> the doctrine of inherency is available only when the prior inherent event can be established as a certainty. That an event may result from a given set of circumstances is not sufficient to establish anticipation....A prior inherent event cannot be established based on speculation, or where a doubt exists (emphasis added). *Ethyl Molded Product Co. v. Betts Package Inc.*, 9 USPQ2d 1001, 1032-33 (E.D. KY 1988).

In addressing this issue, Dr. Hart answers relevant questions as follows in his Expert Declaration dated 2 August 2004:

> 5. What if exogenous FRP were given to intact adult mammals, rather than hypophysectomised juvenile animals – would that cause an absolute reduction in ovarian mass? No, all this might achieve would be a blunting of the mid-cycle rise in the mass of the ovulating ovary, given that the mode of action of FRP is to inhibit gonadotropin action. The potential suppression of a rise in mass of the ovulating ovary is not an absolute reduction in the mass of both ovaries, such as can be readily obtained with exogenous micrin.
>
> 6. Would the administration of exogenous FRP to adult intact mammals be expected to cause an absolute reduction in non-gonadal organ masses, as is achieved with exogenous micrin? Again, no. To say otherwise would be to imply that gonadotropins increase the mass of non-gonadal organs, which is not the case, and ignores the fact that FRP does not even reduce in an absolute sense the mass of an ovulatory ovary; diZerega makes it clear (for example column 11, lines 55-66) that the effect of FRP is to suppress the response to gonadatropins.

As discussed above, it cannot reasonably be stated that the diZerega reference discloses or suggests a material that is induced by clomiphene, obtained post-oestrus and that necessarily reduces organ mass (gonadal or non-gonadal) in live adult mammals. The examiner's speculation as to the "likely" properties of the diZerega material is technically incorrect as well as legally insufficient to support a rejection based on the diZerega reference. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102/103 is respectfully requested.

B. Claims 1, 3-6, 8, 11-14, which are directed to a material that reduces the mass of body organs, including non-gonadal organs of a live adult mammal, and that is inducible by clomiphene and obtained by purifying post-oestrus ovarian venous blood, are not obvious over U.S. Patent No. 4,734,398, because the cited reference does not teach or even suggest a material having the advantageous characteristics of the subject material.

Nothing in the diZerega reference would have led the skilled artisan to the advantageous material claimed by the Appellant. As noted above, apart from the molecular mass, no relevant physical or functional similarities exist between the Appellant's material and the composition described in the diZerega reference.

In order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must find both the suggestion of the claimed invention, and a reasonable expectation of success in making and practicing the invention, in light of the teachings of the prior art. *In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529, 1531, (Fed. Cir. 1988). The diZerega reference does not disclose or suggest the material claimed by the Appellant.

The claimed material is produced from a different source as follows: FRP activity was detected in ovarian venous blood downstream of ovulatory ovaries, but no FRP activity was found when using peripheral blood or ovarian venous blood from the contralateral anovulatory ovary (see column 10 lines 52-57), nor was there any activity in the case of bilaterally anovulatory patients (see column 10 lines 57-60); in contrast, micrin is found in blood from either ovary and is also detectable in bilaterally anovulatory individuals and in peripheral blood. Micrin is also obtained at a different time during the female reproductive cycle, and has the significantly different property of being able to reduce gonadal and non-gonadal organ size - these all go to show that the present invention is novel and nonobvious, and indeed surprising.

A finding of obviousness is proper only when the prior art contains a suggestion or teaching of the claimed invention. Here, it is only the applicant's disclosure that provides such a teaching, and the applicant's disclosure cannot be used to reconstruct the prior art for a rejection under 35 U.S.C. §103. This was specifically recognized by the CCPA in *In re Sponnoble*, 56 CCPA 823, 160 USPQ 237, 243 (1969):

> The Court must be ever alert not to read obviousness into an invention on the basis of the applicant's own statements; that is we must review the prior art without reading into that art appellant's teachings. *In re Murray*, 46 CCPA 905, 268 F.2d 226, 112 USPQ 364 (1959); *In re Sprock*, 49 CCPA 1039, 301 F.2d 686, 133 USPQ 360 (1962). The issue, then, is whether the teachings of the prior art would, in and of themselves and without the benefits of appellant's disclosure, make the invention as a whole, obvious. *In re Leonor*, 55 CCPA 1198, 395 F.2d 801, 158 USPQ 20 (1968). (Emphasis in original)

The diZerega reference does not disclose or suggest a material that is inducible by clomiphene post-oestrus nor does it disclose a material that can reduce organ mass. Rather, diZerega only provides FRP, a material that is not induced by clomiphene and only appears to affect ovaries in their growth response to gonadotropins. Considering this clomiphene point further, it can be pointed out that diZerega investigated the effect of clomiphene treatment in spontaneously menstruating women, the results being shown in diZerega's figure 18. Neither results shown in the figure (follicular fluid inhibitory protein activity and estradiol concentration) show any significant difference between the untreated women and those treated with clomiphene. This shows that clomiphene does not induce FRP production. Thus, the diZerega reference does not describe, teach, nor suggest a material having the unique characteristics of the claimed invention. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §103 based on diZerega is respectfully requested.

In view of the foregoing, the Appellant urges that the Board reverse the 35 USC §102/103 rejections and that this application be passed to issuance.

Respectfully submitted,

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Attachments: Appendix A: Currently Pending Claims

APPENDIX A

1. An endogenous material, inducible in a mammal post-oestrus by clomiphene, and having the ability to reduce the mass of body organs including non-gonadal organs, of a live adult mammal, the material being obtained by:

collecting ovarian venous blood from a female mammal post-oestrus;

preparing ovarian venous plasma from the blood; and

at least partially purifying said material from the plasma to obtain at least a nominal 10-30 kD sub-fraction.

3. The material according to claim 1, wherein the purifying comprises obtaining a 10-20 kD fraction.

4. The material according to claim 3, wherein the purifying additionally comprises ion exchange chromatography, and collecting the fraction eluted in 0.1-0.2 M NaCl.

5. The material according to claim 1, wherein the purifying comprises the following protocol:

clearing plasma by centrifugation;

spinning the cleared plasma to give a nominal 0-30 kD fraction;

spinning the nominal 0-30 kD fraction to give the nominal 10-30 kD sub-fraction;

concentrating and gel-filtering the nominal 10-30 kD sub-fraction to give a nominal 10-20 kD sub-fraction;

concentrating and buffer-diluting the nominal 10-20 kD sub-fraction repeatedly;

applying the concentrate and buffer-diluted nominal 10-20 kD sub-fraction repeatedly to an ion exchange column eluted with a gradient of 0-.3 M NaCl; and

dividing the eluate into 0-0.1 M, 0.1-0.2 M and 0.2-0.3 M NaCl ion exchange fractions.

6. The material according to claim 1, wherein the mammal is a sheep.

8. A pharmaceutical composition comprising an endogenous material_inducible by clomiphene, having the ability to reduce the mass of body organs including non-gonadal organs, the material being obtained by:

collecting ovarian venous blood from a female mammal;

preparing ovarian venous plasma from the blood; and

at least partially purifying said material from the plasma to obtain at least a nominal 10-30 kD sub-fraction

and a pharmaceutically acceptable excipient or carrier.

11. The pharmaceutical composition, according to claim 8, wherein the purifying comprises obtaining the 10-20 kD fraction.

12. The pharmaceutical composition, according to claim 8, wherein the purifying additionally comprises ion exchange chromatography, and collecting the fraction eluted in 0.1-0.2 M NaCl.

13. The pharmaceutical composition, according to claim 8, wherein the purifying comprises the following protocol:

clearing plasma by centrifugation;

spinning the cleared plasma to give a nominal 0-30 kD fraction;

spinning the nominal 0-30 kD fraction to give the nominal 10-30 kD sub-fraction;

concentrating and gel-filtering the nominal 10-30 kD sub-fraction to give a nominal 10-20 kD sub-fraction;

concentrating and buffer-diluting nominal 10-20 kD sub-fraction repeatedly;

applying the concentrated and buffer-diluted nominal 10-20 kD sub-fraction repeatedly to an ion exchange column eluted with a gradient of 0-.3 M NaCl; and

dividing the eluate into 0-0.1 M, 0.1-0.2 M and 0.2-0.3 M NaCl ion exchange fractions.

14. The pharmaceutical composition, according to claim 8, wherein the mammal is a sheep.